Long Term Mortality and Cancer Risk in Irradiated Rhesus Monkeys[1]

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1. The animals involved in this study were procured, maintained and used in accordance with The Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

Running head: Proton Bioeffects

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ABSTRACT

Lifetime observations on a group of 358 rhesus monkeys indicate that life expectancy loss from exposure to protons in the energy range encountered in the Van Allen belts and solar proton events is influenced primarily by the dose rather than by the energy of radiation. After 24 years, life expectancy losses from similar surface doses of low-LET (138-2300 MeV) and high-LET (32-55 MeV) protons are not significantly different, but the high-LET protons are associated with more deaths in the early years, while the low-LET protons contribute more to mortality in later years. In males, the most significant cause of life shortening is nonleukemia cancers. In females, radiation increased the risk of endometriosis (an abnormal proliferation of the lining of the uterus) which resulted in significant mortality in the years before early detection and treatment methods were employed. The findings support the 1989 guidelines of the NCRP for maximum permissible radiation exposures in astronauts.

INTRODUCTION

This report summarizes data from the U. S. Air Force School of Aerospace Medicine Delayed Effects Colony (DEC), a group of rhesus monkeys whose members were exposed to single doses of total body proton irradiation in the years 1964-1969. In the subsequent years, they have been observed and periodically examined for the development of any late effects related to the radiation experience that may influence radiation protection criteria for future military space crews. Nine-year and seventeen-year interim reports have been published (12, 30). This report focuses on those factors that are the primary determinants in radiation risk assessment; namely, life shortening and cancer risk. Data on other radiation related effects are also being accumulated and have been discussed in other publications (13,14,22). The experiment is the only existing lifetime study of the effects of total body proton irradiation in a primate species.

MATERIALS AND METHODS

The animals in this study were wild caught rhesus monkeys of both sexes that were given single, high dose rate, total body surface exposures of monoenergetic protons as part of a series of experiments to determine the relative biological effectiveness of protons in the manifestation of the acute radiation syndrome. The estimated age of the subjects ranged from 18-36 months at time of irradiation, based on body weight and dentition. Sufficient subjects (nearly 2000) were exposed to determine the acute effects and the $LD_{50/30-90}$ for protons of several energies in the range of 5-2300 MeV (4-8, 16,17,26). Additional groups were exposed to high energy electrons and X-rays for comparative purposes. A detailed description of the exposure methodology

can be found in earlier reports (12, 30). The rationale for the selection of the proton energies was that the most significant fraction of the total proton fluence in major solar flare events would come from particles in the 5-100 MeV range, but higher energies were also important because they included the spectrum of galactic cosmic radiation (3). A practical consideration was the existence and availability of radiation sources capable of performing primate total body surface exposures. Figure 1 shows the dose ranges for the four single proton energies used in this study converted to proton fluences on the same scale as the total integrated fluxes for three large solar proton events.

(Figure 1)

During an isotropic exposure, as would occur in the space radiation environment, some protons with energies of less than 100 MeV do not completely penetrate the body of a small rhesus monkey. The ionization density along the path of penetration increases up to a maximum, the Bragg Peak, then falls sharply, with deeper tissues receiving no direct radiation from the energetic particle. This pattern is significant in the interpretation of biological effects data, therefore; we have combined data from the groups representing nonhomogeneous dose (32 and 55 MeV) and homogeneous dose (138, 400 and 2300 MeV) distributions for statistical analysis. When making comparisons between these energy groups, we have referred to energetic particles that transfer 100% of their kinetic energy within the body volume of the monkey as high-LET, and those that do not as low-LET.

Among those animals that survived the 100-day postirradiation observation period were 301 monkeys that made a satisfactory recovery and were considered suitable candidates for extended observation. These animals, together with 57 age-matched nonirradiated monkeys, were retained for a

longitudinal survey of delayed effects. The exposure data for all animals selected for long term observation are summarized in Table I.

(Table I)

At the present time, the surviving animals are examined at six-month intervals. The examinations include routine hematology and biochemistry profiles and slit-lamp ophthalmoscopy. No animals are euthanatized except for humane considerations, and all animals that die receive a thorough post-mortem examination.

RESULTS

Mortality The initial acute studies by Dalrymple, et al. (7) and Lindsay, et al. (17), revealed that particles with insufficient energy to penetrate the total body thickness require higher surface doses to induce lethality during the acute radiation sickness phase (within 100 days postirradiation); however, the relationship of energy to long term lethality appears to be somewhat different. As shown in Figure 2, the high dose animals in both energy groups had a similar survival probability at the 22-year point, but the low energy (high LET) exposed monkeys had higher mortality in the first ten-year period ($p<.001$, Breslow's test), while the high energy exposed animals experienced greater mortality in the later phase of the study. The widest spread in the survival probability among the groups was observed at approximately 14 years after irradiation. Mortality in the control group began to accelerate at the 16-year point and the survival probability of the controls is now similar to that of the two low-dose groups. The median age at death for nonirradiated rhesus monkeys in our colony is approximately 24 years.

(Figure 2)

Causes of death in the irradiated and control populations are compared in Figure 3.

(Figure 3)

Here, one of the most striking observations is that endometriosis has been the leading killer of irradiated females, while cancer retains that distinction in irradiated males (25, 27). Although any adult female rhesus monkey is susceptible to development of endometriosis that is morphologically similar to the human disease (18), irradiated females have a higher incidence than the controls. Whether it is spontaneous or radiation-induced, untreated endometriosis in monkeys is often life-threatening due to the size and invasiveness of the lesions. This prognosis rarely applies for humans. Most of the mortality attributable to endometriosis occurred in the earlier cases before rapid detection and treatment methods were employed (10). Endometriosis did not appear in the colony until the sixth year after irradiation, indicating that it is a disease of mature females and that cases attributable to radiation have a long latent period. Since endometriosis is not normally life threatening in humans, we have included calculations that ignore the contribution of endometriosis to the loss of life expectancy.

The method of Cohen and Lee (2) was used to determine the life expectancy loss due to radiation exposure by comparing life expectancies in irradiated subjects and age matched controls. Figure 4 illustrates the life shortening effect of each of the four combinations of proton energy and dose.

(Figure 4)

To facilitate estimates of life expectancy loss from solar proton radiation, we have fitted separate curves to the dose response data for

partially penetrating (55-MeV) and totally penetrating (138, 400 and 2300 MeV) protons (Figure 5).

(Figure 5)

The similarity in the curves suggests that, although the radiation related deaths may occur earlier with the protons that have a nonhomogeneous or "Bragg peak" dose distribution, the overall effect on life expectancy is more closely related to the absorbed dose than to the energy of the particle.

Cancer A summary of all fatal cancers is given in Table II.

(Table II)

The first case was a brain tumor in a male irradiated with 8.0 Gy of 55-MeV protons that occurred 13 months after exposure. The most recent case was a similar tumor occurring in a male exposed to 2-MeV X-rays nearly 24 years before the expression of the malignancy. Table III summarizes the latency of the cancers by original tissue type.

(Table III)

Tumors of epithelial origin (carcinomas and adenomas) had a longer average latent period than those of mesothelial origin (connective or neuroglial tissues). Epithelial tumors were the only type observed in the control population, which did not experience a fatal cancer until the 18th year of observation.

The cumulative cancer incidence by energy group is given in Table IV. Incidence densities (cancers per monkey-year at risk) have been compared using Poisson statistics to determine the null chi square value (19).

(Table IV)

Cancer outweighed other pathological conditions as a cause of death for animals receiving higher radiation doses irrespective of energy, as shown in Table V.

(Table V)

We have used Kaplan-Meier product-limit estimates to determine the probability that any animal death will be due to cancer during a 288-month post exposure period. The results are shown in Figure 6.

(Figure 6)

Although the number of cases in the controls is small, it is evident that the risks that any deaths will be due to cancer in both populations converged at approximately the 20-year point and have subsequently increased at nearly the same rate. Males were more likely to die of cancer than females, as shown in Figure 7.

(Figure 7)

Because the 1970 NAS radiation protection standards for astronauts were based on an estimate of the absorbed dose required to double the number of fatal cancers in the exposed population, we applied a conservative linear model to estimate the cancer doubling doses for space radiations. We made separate estimates for high-LET and low-LET radiations based on the surface absorbed dose, ignoring any quality factors. The 72 animals that received 55-MeV proton radiation are the largest group that were exposed to high-LET radiation. The cancer incidence in this group is shown in Figure 8. Regression lines were calculated by the method of Cochran and Cox (1), both including and excluding dose groups with no cancers. In either case, the dose effect is significant by the chi squared test ($p<.005$). When the zero dose groups are included, the calculated dose required to double the incidence of

fatal cancer over the 24-year observation period is 2.26 Gy.

(Figure 8)

The estimates for low-LET radiations are shown in Figure 9. These data include the cancer incidence in groups exposed to high energy X-rays or protons with energy greater than 100 MeV.

(Figure 9)

When the control group is included, the dose effect is not statistically significant ($p>0.1$), but we have indicated the regression lines that estimate that the dose required to double the estimated natural incidence of cancer would be 4.54 Gy. The most prevalent single type of cancer was the malignant brain tumor described by pathologists as Grade IV astrocytoma or glioblastoma multiforme. Nine of these tumors occurred in the animals exposed to 55-MeV protons in doses from 4 to 8 Gy with latent periods from 13 months to 20 years (Table VI)(29).

(Table VI)

Revised depth-dose estimates for 55-MeV protons using computed tomography in monkey head phantoms has shed some light on the unusual incidence in this group. Isodose maps constructed by Leavitt (15) for a monkey exposed to a unidirectional beam of 55-MeV protons while being rotated on the longitudinal axis of the body revealed that overlapping of the areas where the peak energy distribution occurred created "hot spots" that received as much as three times the surface absorbed dose of radiation. This discovery may explain why 55-MeV protons appear to be much more effective than therapeutic X-rays in the induction of intracranial neoplasms (Table VII)(21).

(Table VII)

DISCUSSION AND CONCLUSIONS

Life expectancy loss is a convenient measure for assessment of radiation risk relative to that of other environmental hazards. As we reported at the 20-year point in the study, for the dose range of 0.5-8.0 Gy total body surface radiation, the average life expectancy loss from all types of space radiation was 200 to 500 monkey-days or 500 to 1250 person-days per Gy (28). The NCRP has recommended new career dose limits for astronauts between the ages of 25 and 55 years, based on excess cancer mortality in both sexes. These limits range from 1.0-3.0 Svt in females and 1.5-4.0 Svt in males (11, 24). Assuming a 2.0 Gy career dose and ignoring dose rate effects for a "worst case" estimate, our findings would translate this exposure into an average life expectancy loss of 1000 to 2000 days. Equivalent nonradiation hazards are: being a coal miner (1100 days); being 30% overweight (1300 days); having heart disease (2100 days). The risk is less than that for a cigarette smoking male (2250 days) but greater than that fora cigarette-smoking female (800 days)(2).

The difference in cancer incidence between energy groups emphasizes the uncertainty in the application of dose limits for space radiation exposures when the energy spectrum is unknown. When the most conservative linear fits are applied to our dose-response data, our results support the recent recommendations by the NCRP for lowering the astronaut dose limits (11). It must be borne in mind that our monkeys were irradiated as juveniles in a stage of development that would roughly correspond to that of an 8 to 10-year-old human being. The atomic bomb casualty data indicate that the relative risk of nonleukemia cancer at 1.0 Gy total body dose decreases with increasing age at time of exposure; the most dramatic change occurs between the two lowest age

groups, 0-9 yrs (relative risk = 2.3) and 10-19 yrs (relative risk = 1.4) (20). These age groupings make it difficult to decide where to include our monkeys when attempting to make a monkey-to-man extrapolation. Since it is more prudent to err on the side of conservatism, we should probably compare our 1.5 to 3-yr-old monkeys with the 10 to 19-yr-old humans at the time of the atom bomb. By adopting this method, we would not overestimate the risk in the next two age groups (the ages that would bracket most space crew members) by more than 15%.

The sex-specific cancer risk analysis (Fig. 7) appears to be at variance with the atomic bomb casualty data which indicate no difference in relative risk associated with gender (23). This comparison could be misleading, however, because our analysis assumes that cancer is unrelated to other causes of death, therefore; those other causes are disregarded in the determination of probability of death due to cancer. If the same genetic factors that predispose individuals to radiation-induced cancer are also associated with increased risk of endometriosis, it is entirely possible that many of the high-risk females succumbed first to endometriosis, leaving a more cancer-resistant population.

Another inconsistency with the atomic bomb survivors is the scarcity of leukemia cases in the monkeys. A single case of acute leukemia occurred in a male 38 months after exposure to 1.0 Gy, 400-MeV protons. Given the age of the subjects at exposure, the atomic survivor data suggest that a significant number of early leukemias could have been expected in the monkeys. We have always assumed that the dose distribution for the 55-MeV protons included most, if not all of the bone marrow, as described in the original dosimetry

calculations. Work is now under way to verify this dose distribution in the manner of the revised brain dosimetry.

Monkeys exposed to the partially penetrating 55-MeV protons developed intracranial tumors at more than twice the rate of their counterparts exposed to similar surface doses of totally penetrating radiation. Also, these tumors were more likely to be malignant. Revised dosimetry estimates on the 55-MeV monkeys indicate that about 55% of the brain volume absorbed from one to three times the surface dose, and the remaining 45% absorbed doses from zero to the surface measurement (15). Although the evidence is strong that the high glioblastoma incidence is a dose effect, related to the Bragg peak energy distribution, there could be other factors involved. Early results of in-vitro studies by Wigle (USAFSAM, unpublished data) suggest that 55-MeV protons can induce sensitivity to subsequent radiation damage in monkey cells and that the relative biological effectiveness for this induced sensitivity may be greater than that of the low-LET radiations. If it is verified, this observation might help explain the extremely short latent period of several of the glioblastomas since most human glioblastomas of juveniles that fulfill the criteria for being radiation induced have latent periods of ten or more years (9, 31). As in the general human population, the glioblastomas occurred more frequently in males, but the difference was not statistically significant because of the limited numbers and the unequal sex distribution in the monkey population. When the risk of brain tumors associated with 55-MeV protons is compared with that of human X-ray therapy patients, the cases per unit of surface absorbed dose is over twenty times greater with the protons. This difference is certainly sufficient to warrant additional study of the mutagenic potential of partially penetrating protons that have a high linear

energy transfer at a tissue depth corresponding to that of the human central nervous system.

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TABLE I

RADIATION EXPOSURE DATA FOR ALL MONKEYS ON LIFETIME OBSERVATION

Type	Energy (MeV)	Dose Range (Gy)	Date	Irradiated M	Irradiated F	Control M	Control F
Proton	5	N/A [a]	67-69	0	0	8	5
Proton	32	2.8-5.6	Jul 64	6	6	0	1
Proton	55	0.25-8.0	Apr 65	50	22	6	0
Proton	138	2.1-6.5	Jan 65	19	13	3	4
Proton	400	0.5-6.0	Mar 65	28	27	5	5
Proton	2300	0.56-5.6	Oct 65	21	25	6	1
X-ray	2	4.46-7.16	Mar 64	15	17	0	2
Electron	2	9.0-15.5	Nov 69	5	7	1	3
Electron	1.6	10.0-15.0	May 68	0	12	0	0
Proton	10 & 100 [b]	3.0-12.0	Apr 69	17	11	5	2
			Total:	161	140	34	23

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a. The 5 MeV proton exposures were short term experiments. No irradiated survivors were retained for extended observation. Some controls from these studies were used to augment the controls from the electron and mixed proton studies because they were from the same age group.

b. Mixed proton exposures designed to approximate solar flare energy distributions. The ratio of flux densities was 9:1 (10-MeV:100-MeV).

TABLE II

FATAL CANCERS IN THE DELAYED EFFECTS COLONY

SEX	TYPE	MeV	Gy	ORGAN	TUMOR TYPE	LATENCY (Mo)
M	Proton	55	8.0	Brain	Glioblastoma	13.2
M	Proton	55	6.0	Brain	Glioblastoma	17.2
M	Proton	400	1.0	Reticuloendothelium	Acute leukemia	32.7
M	Electron	1.6	15.0	Subcutis (Leg)	Fibrosarcoma	40.5
M	Proton	55	8.0	Brain	Glioblastoma	42.9
M	Electron	1.6	15.0	Subcutis (Leg)	Fibrosarcoma	54.3
M	Proton	55	6.0	Subcutis (Leg)	Fibrosarcoma	54.5
M	Proton	55	6.0	Brain	Glioblastoma	54.8
M	Electron	1.6	15.0	Kidney	Adenosarcoma	55.1
M	Proton	55	8.0	Brain	Glioblastoma	59.5
M	Proton	2300	3.95	Subcutis	Sarcoma	71.7
M	Proton	55	2.0	Bone (Mandible)	Sarcoma	85.4
M	Proton	55	4.0	Brain	Glioblastoma	93.5
F	Proton	55	6.0	Brain	Glioblastoma	99.7
M	Proton	Mixed	12.0	Subcutis (Leg)	Fibrosarcoma	108.1
M	Proton	55	6.0	Mucosa (Nasal)	Carcinoma	116.4
M	Proton	138	5.0	Muscle	Sarcoma	122.6
F	X-ray	2	5.38	Subcutis (Elbow)	Sarcoma	127.5
M	Proton	400	4.0	Myocardium	Sarcoma	135.4
M	X-ray	2	7.16	Kidney	Carcinoma	144.4
M	Proton	55	6.0	Brain	Glioblastoma	147.5
M	Proton	138	3.6	Subcutis	Fibromyxosarcoma	159.2
F	Proton	Mixed	12.0	Spinal cord	Glomangioma	168.3
M	Proton	Mixed	9.0	Lung	Carcinoma	180.7
M	Proton	400	4.0	Subcutis (Arm)	Sarcoma	181.1
M	Proton	138	2.1	Prostate	Adenocarcinoma	186.9
M	X-ray	2	5.38	Pancreas	Adenocarcinoma	188.5
M	Proton	Mixed	6.0	Kidney	Adenocarcinoma	189.8
M	X-ray	2	7.16	Small Intestine	Adenocarcinoma	197.3
F	Proton	138	3.6	Liver	Hepatocarcinoma	205.8
M	Nonirradiated control			Skin	Carcinoma	213.3
M	Proton	138	5.0	Kidney	Adenoma	214.2
F	Proton	138	3.6	Small Intestine	Adenocarcinoma	215.3
F	Nonirradiated control			Mammary Gland	Adenocarcinoma	222.2
M	Proton	138	5.0	Bone (Spine)	Osteosarcoma	217.0
F	Proton	2300	2.25	Brain	Meningioma	226.6
F	Proton	32	5.6	Small Intestine	Adenocarcinoma	234.3
M	Nonirradiated control			Small Intestine	Adenocarcinoma	236.4
M	Proton	55	4.0	Brain	Glioblastoma	238.2
M	Proton	138	2.1	Adrenal cortex	Adenoma	239.7
F	Nonirradiated control			Colon	Adenocarcinoma	246.7
M	X-ray	2	6.24	Brain	Ependymoma	248.1
F	Proton	55	4.0	Reticuloendothelium	Lymphosarcoma	258.7
F	Nonirradiated control			Thyroid	Carcinoma	260.8
M	Proton	55	4.0	Small Intestine	Adenocarcinoma	267.1
M	Proton	400	1.0	Ileum	Adenocarcinoma	278.6
F	X-ray	2	4.46	Small Intestine	Adenocarcinoma	285.7
M	X-ray	2	6.24	Brain	Glioblastoma	286.4

TABLE III

MEAN LATENT PERIOD BY TISSUE OF ORIGIN

Tissue	Cases	Mean Latent Period	Std Dev
Connective	17	123.4 mo	69.9
Neural	10	120.1 mo	102.9
Epithelial	15	209.6 mo*	46.84

*$p<.004$ by Student's "t" test with pooled estimate of variance

TABLE IV

INCIDENCE OF MALIGNANT TUMORS

Radiation Type	Median Dose (Gy)	Number Cases	Monkey Years	Incidence Density	Relative Risk	Chi Sq	P
Control	0.00	5	1016	4.92×10^{-3}	1.00		
32 MEV	5.60	1	234	4.27×10^{-3}	0.87	0.02	NS
55 MEV	4.00	14	1039	1.35×10^{-2}	2.74	4.34	<.05
138 MEV	5.00	8	476	1.68×10^{-2}	3.43	4.59	<.05
400 MEV	2.00	4	900	4.44×10^{-3}	0.91	0.02	NS
2300 MEV	2.25	2	779	2.57×10^{-3}	0.52	0.67	NS
X-ray	5.38	7	439	1.59×10^{-2}	3.25	3.86	<.05
Electron	12.00	3	301	9.97×10^{-3}	2.02	0.82	NS
Mixed H+	4.50	4	464	8.62×10^{-3}	1.76	0.66	NS
Hi-LET[a]	4.00	15	1273	1.18×10^{-2}	2.40	3.33	<.10
Lo-LET[b]	2.25	21	2594	8.10×10^{-3}	1.65	1.15	NS
All Irrad	4.00	43	4632	9.28×10^{-3}	1.89	2.29	NS

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a. All animals exposed to partially penetrating protons (32, 55 MeV).

b. All animals exposed to totally penetrating radiations (138-2300 MeV protons and 2 MeV X-rays).

TABLE V

CANCER MORTALITY VERSUS OTHER MORTALITY BY DOSE GROUP (ALL ENERGIES)

Dose (Gy)	Monkey-Yrs	Cancer Deaths	Other Deaths	Cases/1000 M-Y Cancer	Cases/1000 M-Y Other	Ratio	Chi Sq	p
0.0	1015.9	5 (8.8%)	23 (40.4%)	4.92	22.6	0.22	0.7	NS
0.25-2.80	2052.4	6 (5.2%)	64 (55.7%)	2.92	31.2	0.09	0.7	NS
3.00-6.50	1978.8	26 (21.0%)	73 (58.9%)	13.1	36.9	0.36	5.31	<.025
7.16-8.00	79.7	5 (20.8%)	19 (79.2%)	62.7	238	0.26	9.59	<.005
9.00-15.0	552.5	6 (15.8%)	15 (39.5%)	10.9	27.1	0.40	1.66	NS

TABLE VI

GLIOBLASTOMA INCIDENCE IN IRRADIATED MONKEYS

Radiation:	2-MEV X-rays	55-MEV Protons		
Dose:	6.4 Gy	4.0 Gy	6.0 Gy	8.0 Gy
Cases (Males/Females):	1/0	1/0	4/1	3/0
Mean Latent Period:	286 Mo.	93 Mo.	113 Mo.	38 Mo.
Range:	-	-	17-247	13-60
Standard Deviation:	-	-	80	19

TABLE VII

HEAD AND NECK TUMORS IN IRRADIATED POPULATIONS

Group	Subjects	Cases	Years	Avg Dose (Gy)	Tumors/Gy/Yr/10,000
Human Tinea Capitis Patients (100 Kv X-ray Exposures)	10834	56 (16 malignant)	283,390	1.5	1.32
Low-LET Monkey Exposures (138-2300 MeV Proton, X-Ray)	165	9 (1 malignant)	2594	3.4	10.2
High-LET Monkey Exposures (55-MeV Proton)	72	10 (9 malignant)	1039	3.5	24.7

FIGURE CAPTIONS

Figure 1. Proton fluences in our experimental monkey exposures compared with large productive solar flares. The floating bars represent the range of surface absorbed doses of the five monoenergetic protons converted to total fluence. The time integrated proton flux spectra for the three major solar proton events are taken from NASA Technical Paper 2869, December, 1988.

Figure 2. Kaplan-Meier product-limit estimates of the probability of survival after total body proton irradiation with each of four combinations of dose and energy ranges.

Figure 3. Primary causes of death in irradiated and control populations according to sex.

Figure 4. Life expectancy loss from all causes of death for the 24-year postirradiation period (paired sex controls). Group A: 32-55 MeV, 0.26-2.8 Gy; Group B: 138-2300 MeV, 0.25-2.8 Gy; Group C: 138-2300 MeV, 3.6-8.0 Gy; Group D: 32-55 MeV, 3.6-8.0 Gy.

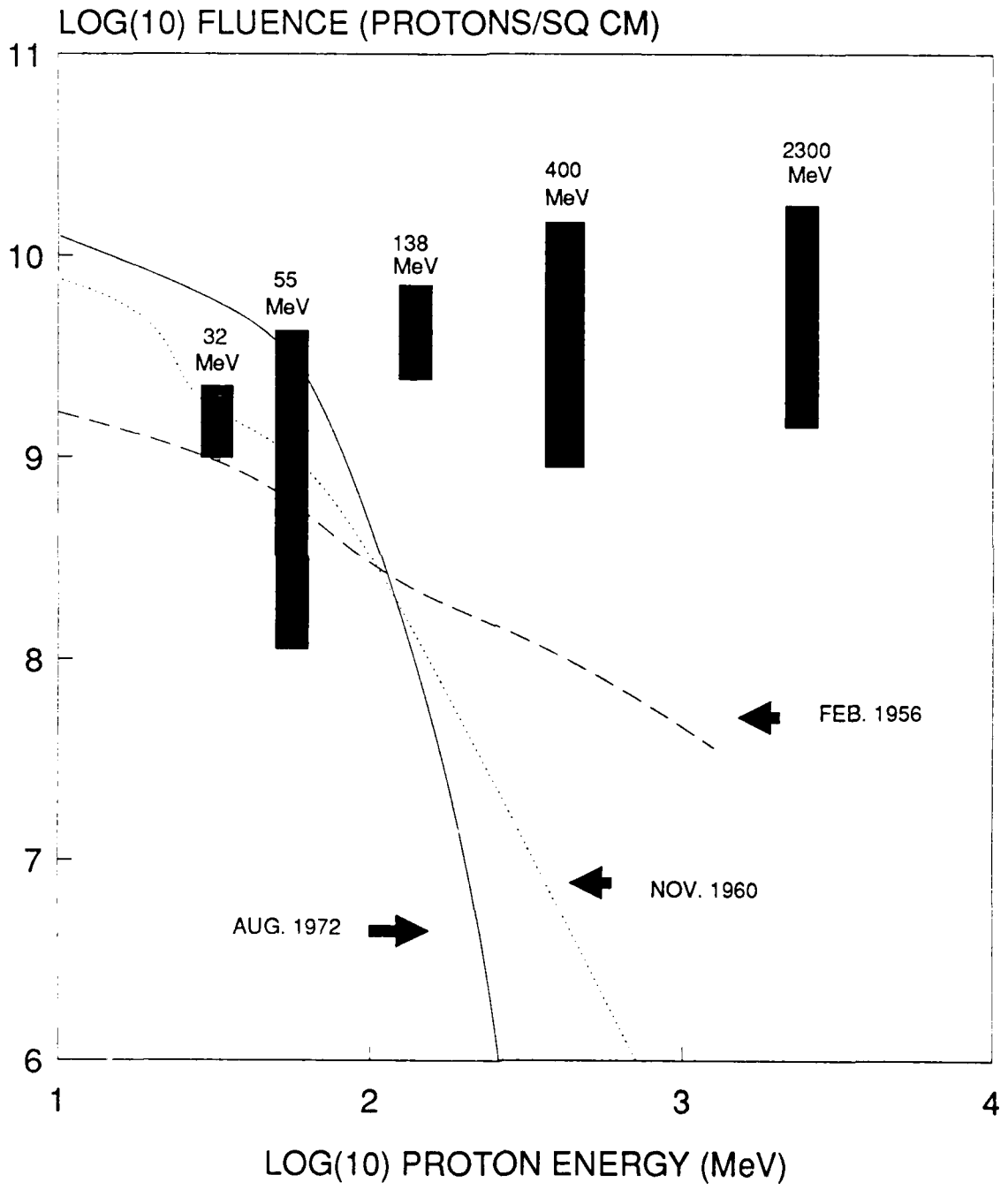
Figure 5. Estimated life expectancy loss from exposure to space radiation.

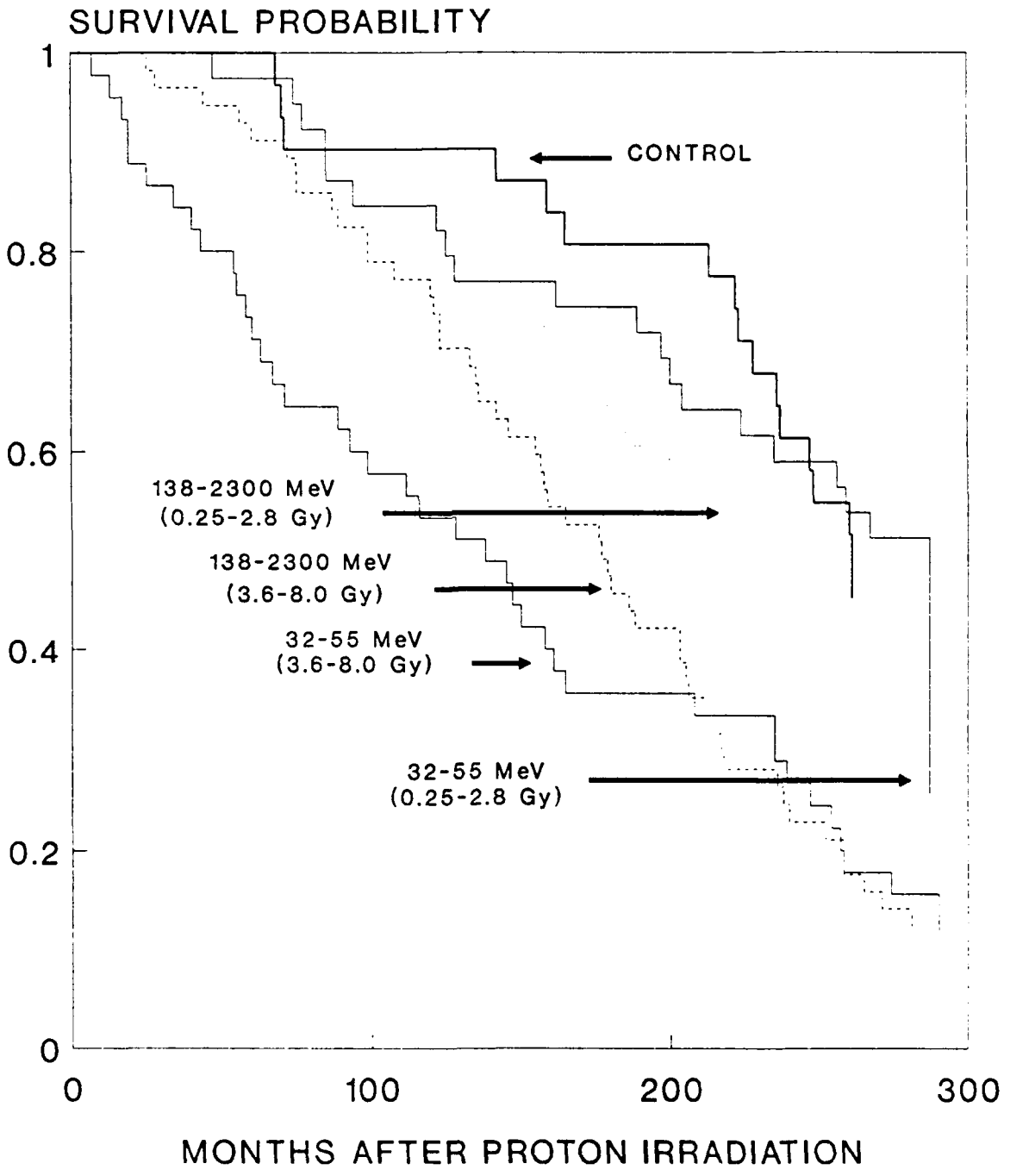
Figure 6. The probability that death at any point during the observation period is due to cancer, based on Kaplan-Meier product-limit estimates.

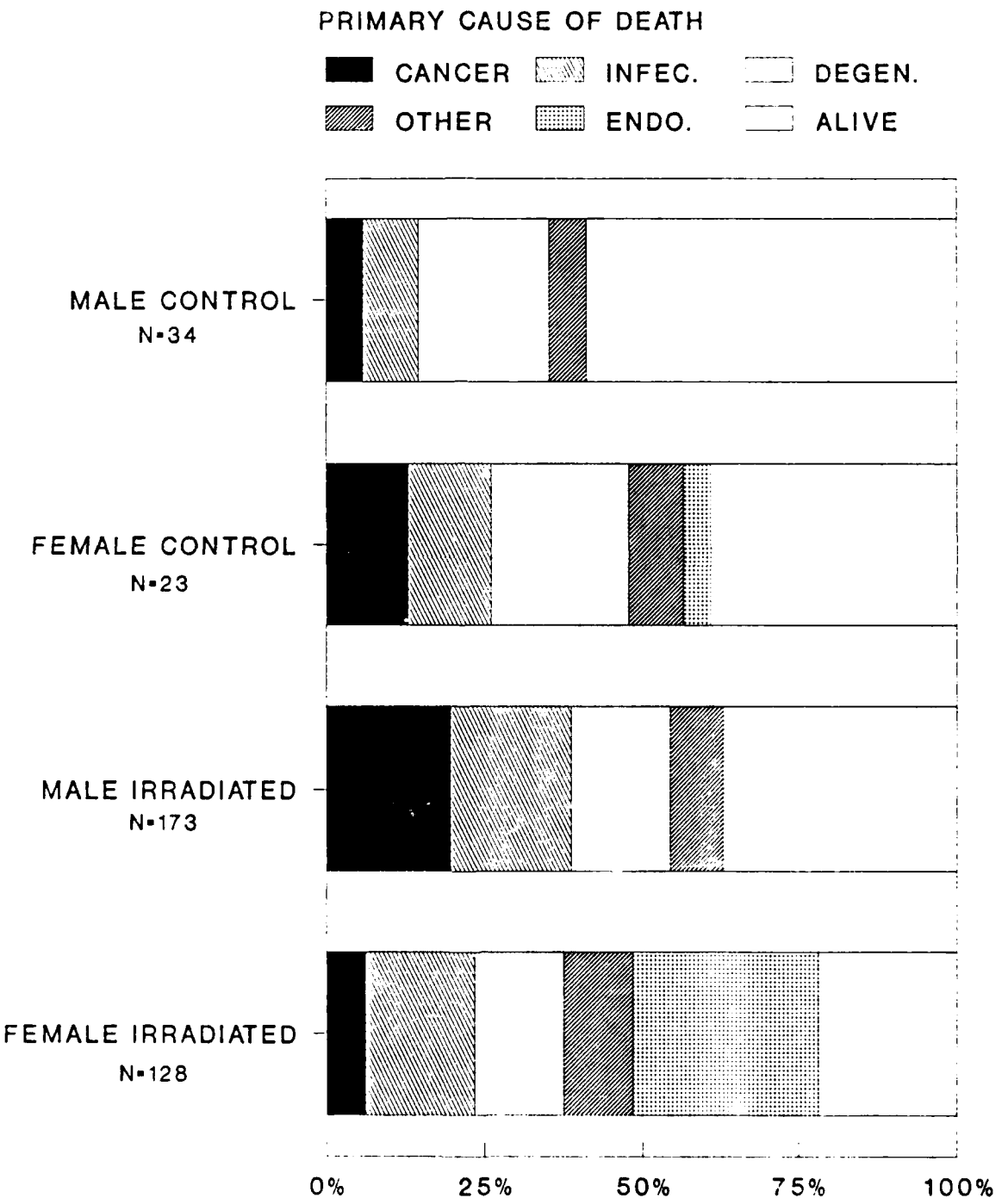
Figure 7. Sex-specific cancer risk. The curves represent the probability that any individual in the original population will escape death by cancer for the given time interval.

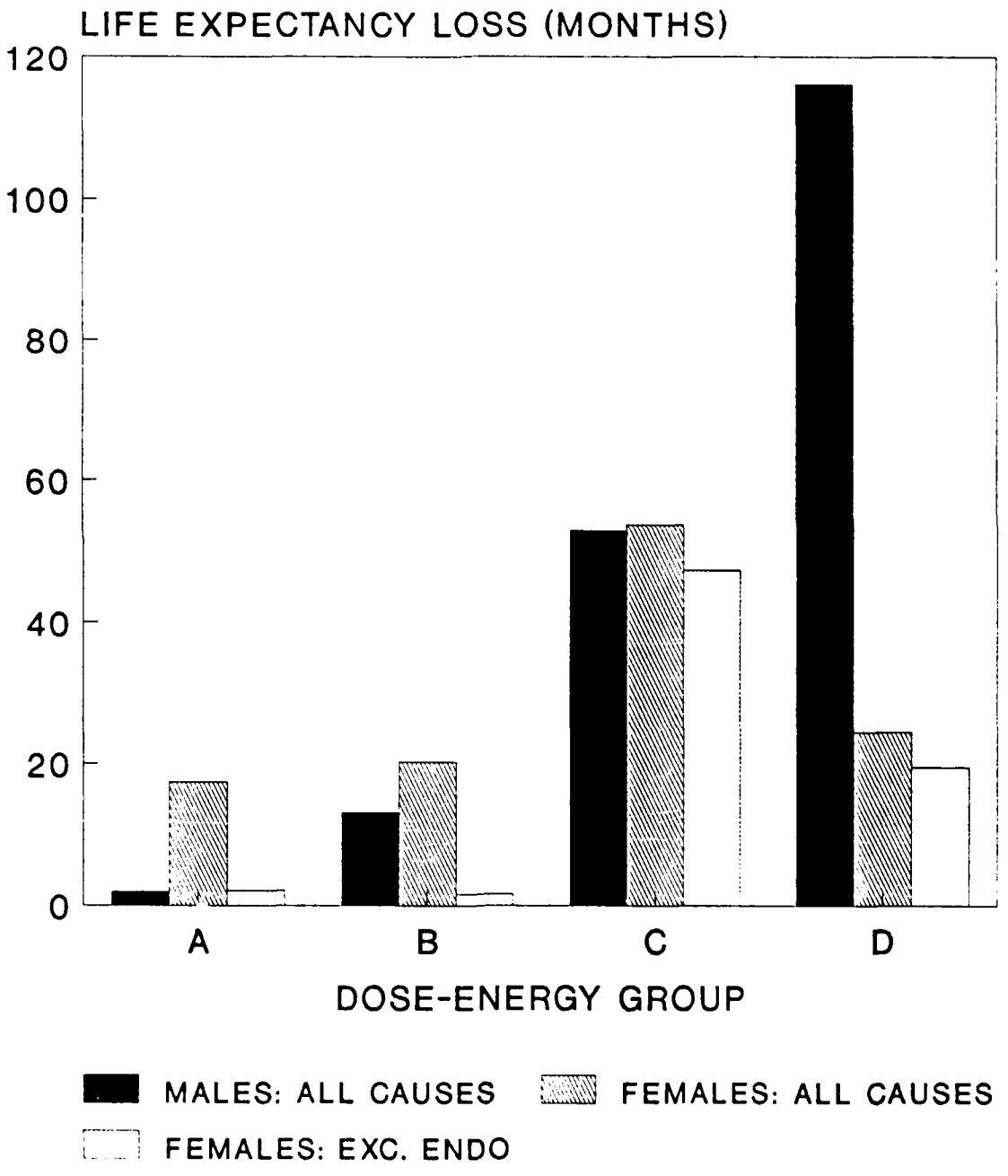
Figure 8. Dose-response estimates for fatal malignancies in high-LET (55-MeV) proton exposed monkeys over a 24 year period using a linear regression model. The estimated doubling dose is 2.26 Gy.

Figure 9. Dose-response estimates for fatal malignancies in low-LET proton and X-ray exposed monkeys over a 24 year period using a linear regression model. The estimated doubling dose is 4.54 Gy.

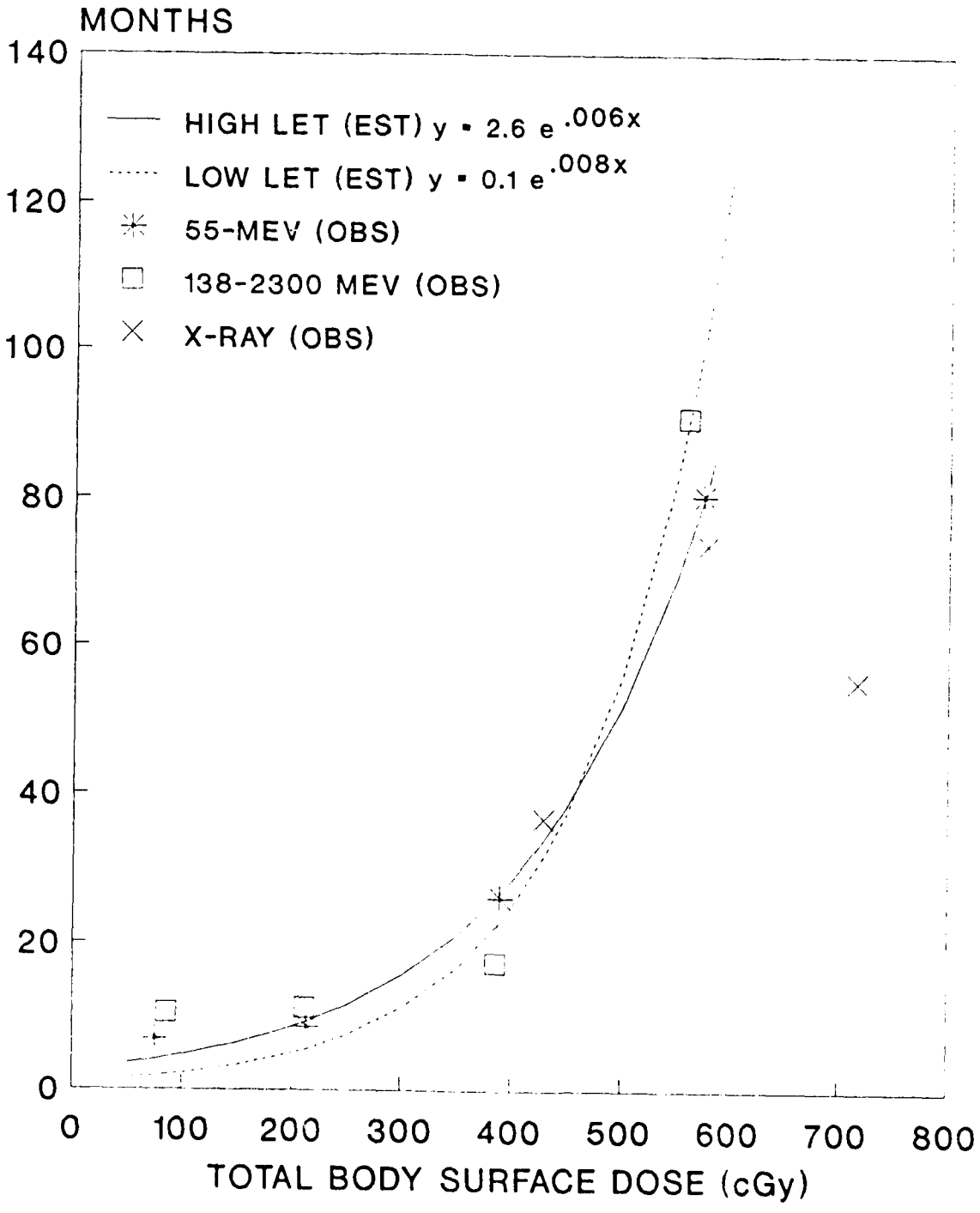

LOG(10) FLUENCE (PROTONS/SQ CM)
11
10
9
8
7
6
1
2
3
4
LOG(10) PROTON ENERGY (MeV)
32 MeV
55 MeV
138 MeV
400 MeV
2300 MeV
FEB. 1956
NOV. 1960
AUG. 1972

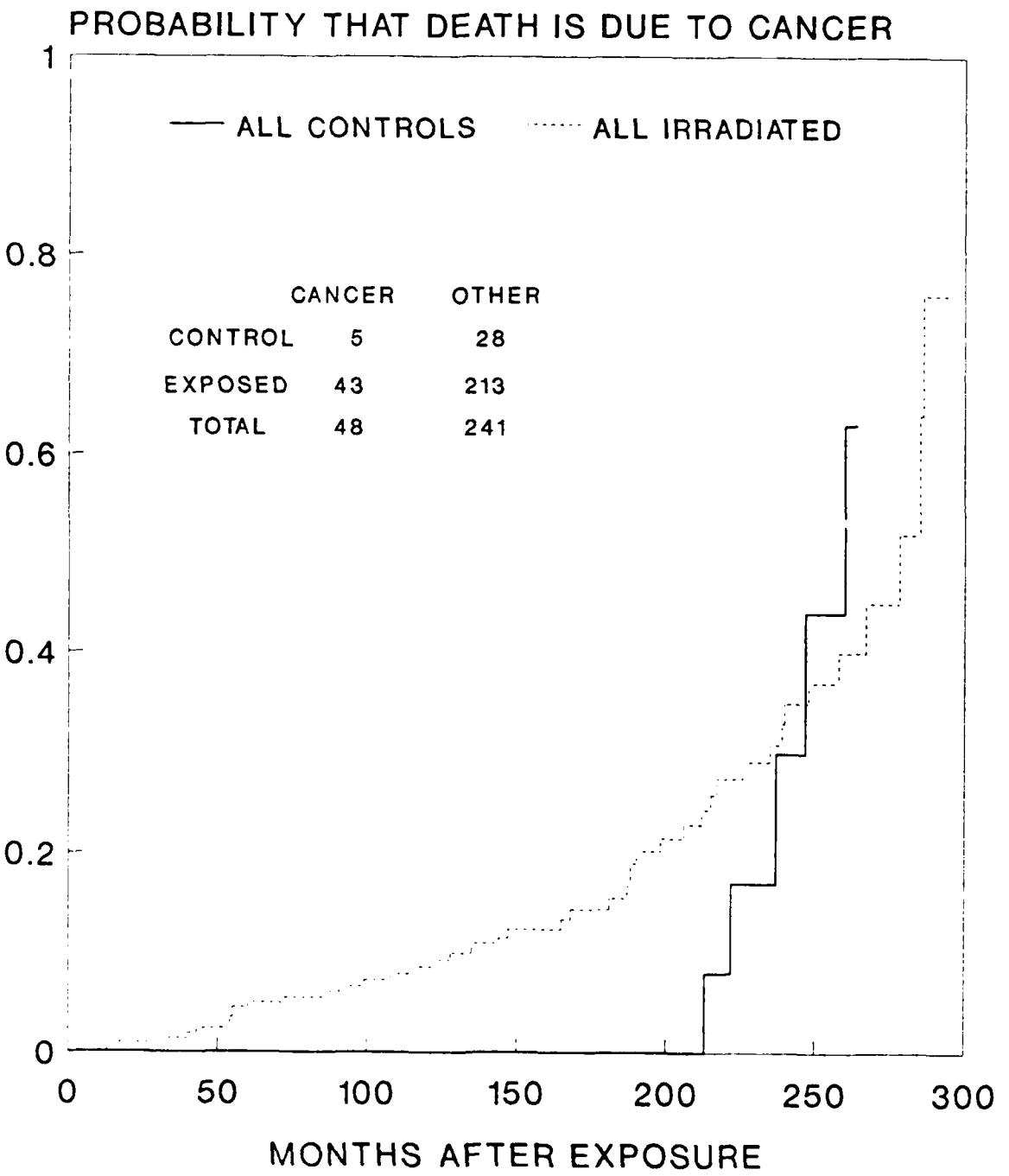

SURVIVAL PROBABILITY
1
0.8
0.6
0.4
0.2
0
CONTROL
138-2300 MeV
(0.25-2.8 Gy)
138-2300 MeV
(3.6-8.0 Gy)
32-55 MeV
(3.6-8.0 Gy)
32-55 MeV
(0.25-2.8 Gy)
0
100
200
300
MONTHS AFTER PROTON IRRADIATION

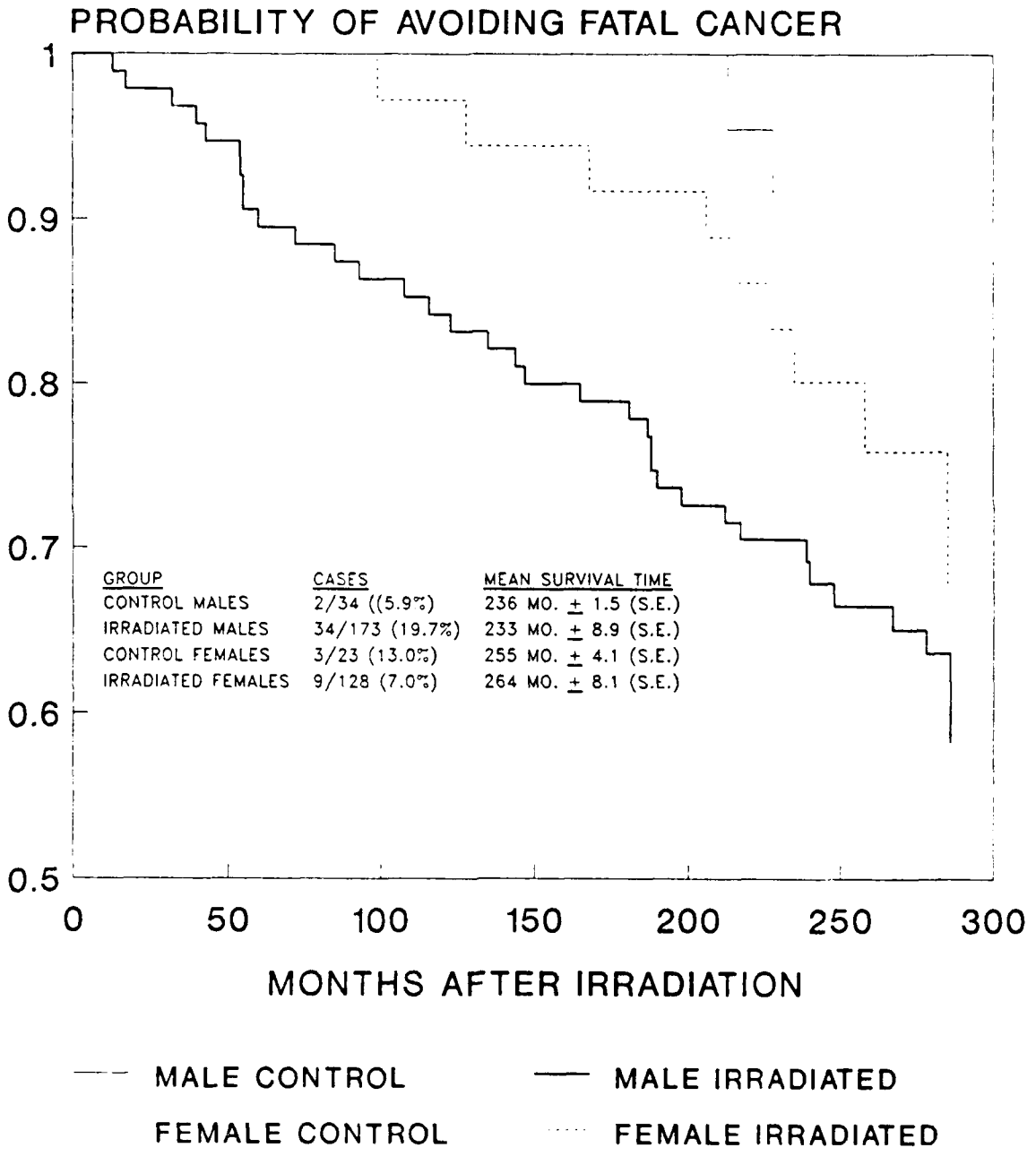

PRIMARY CAUSE OF DEATH
CANCER
INFEC.
DEGEN.
OTHER
ENDO.
ALIVE
MALE CONTROL
N=34
FEMALE CONTROL
N=23
MALE IRRADIATED
N=173
FEMALE IRRADIATED
N=128
0%
25%
50%
75%
100%

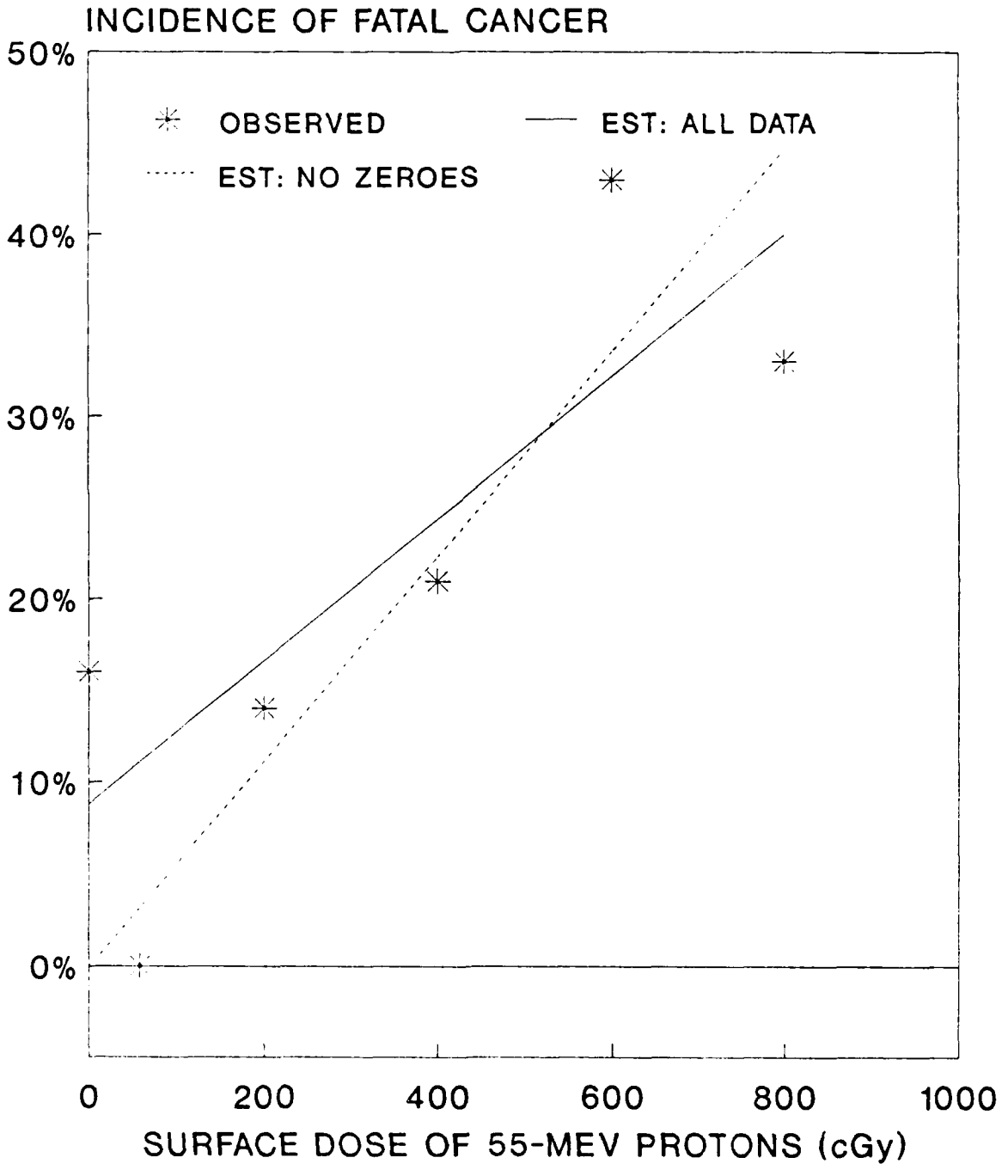

LIFE EXPECTANCY LOSS (MONTHS)
120
100
80
60
40
20
0
A
B
C
D
DOSE-ENERGY GROUP
MALES: ALL CAUSES
FEMALES: ALL CAUSES
FEMALES: EXC. ENDO

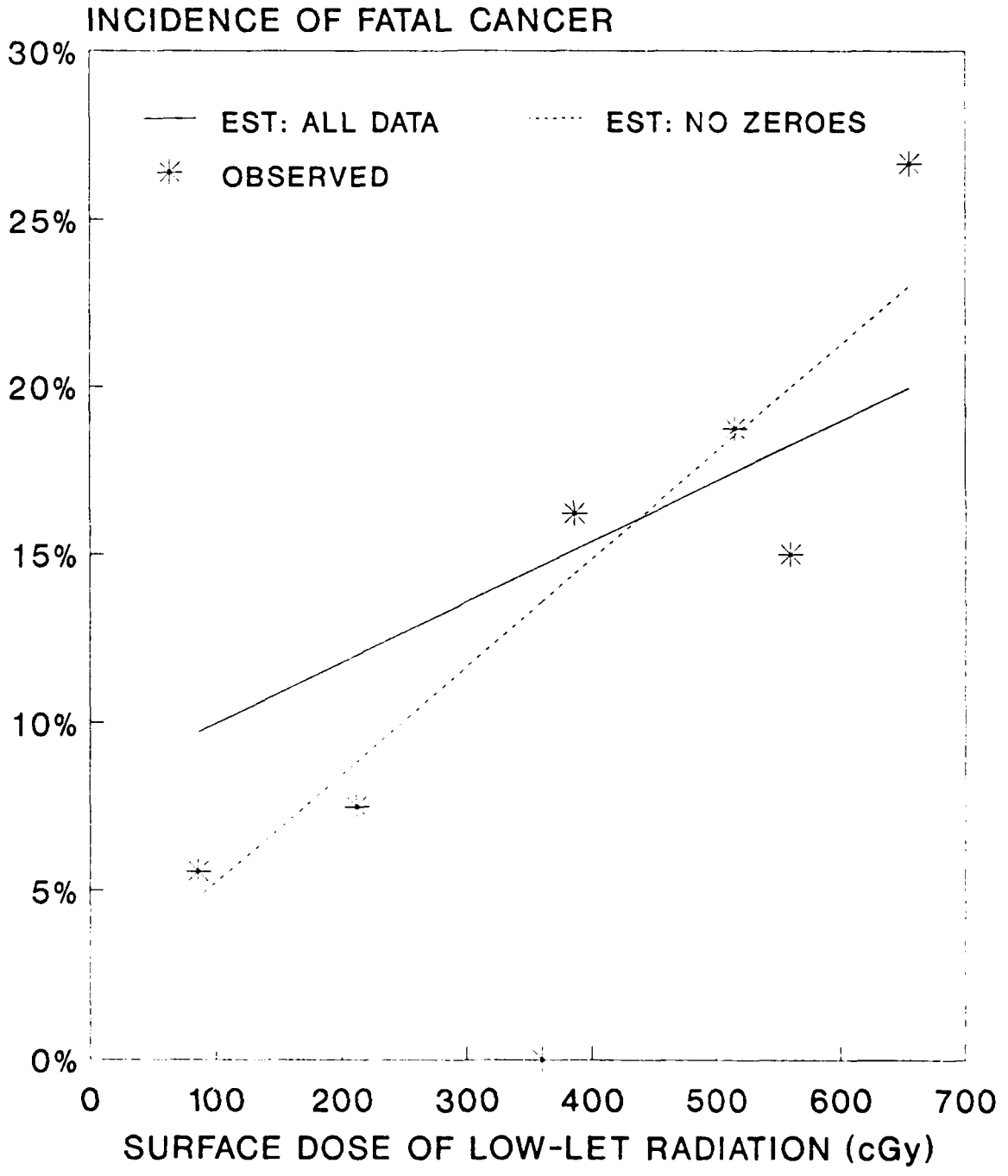
Rad. Res. DH Wood Figure 5




PROBABILITY THAT DEATH IS DUE TO CANCER
ALL CONTROLS
ALL IRRADIATED
CANCER OTHER
CONTROL 5 28
EXPOSED 43 213
TOTAL 48 241
1
0.8
0.6
0.4
0.2
0
0 50 100 150 200 250 300
MONTHS AFTER EXPOSURE


PROBABILITY OF AVOIDING FATAL CANCER
1
0.9
0.8
0.7
0.6
0.5
0
50
100
150
200
250
300
MONTHS AFTER IRRADIATION
GROUP
CASES
MEAN SURVIVAL TIME
CONTROL MALES
2/34 ((5.9%)
236 MO. ± 1.5 (S.E.)
IRRADIATED MALES
34/173 (19.7%)
233 MO. ± 8.9 (S.E.)
CONTROL FEMALES
3/23 (13.0%)
255 MO. ± 4.1 (S.E.)
IRRADIATED FEMALES
9/128 (7.0%)
264 MO. ± 8.1 (S.E.)
MALE CONTROL
MALE IRRADIATED
FEMALE CONTROL
FEMALE IRRADIATED


INCIDENCE OF FATAL CANCER
50%
40%
30%
20%
10%
0%
OBSERVED
EST: ALL DATA
EST: NO ZEROES
0
200
400
600
800
1000
SURFACE DOSE OF 55-MEV PROTONS (cGy)


INCIDENCE OF FATAL CANCER
30%
25%
20%
15%
10%
5%
0%
EST: ALL DATA
EST: NO ZEROES
OBSERVED
0
100
200
300
400
500
600
700
SURFACE DOSE OF LOW-LET RADIATION (cGy)